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INT CL[7] **A61K**
Other: **EPODOC, JAPIO, WPI**

(54) Abstract Title: **Stabilisation of pharmaceutical compositions comprising ACE inhibitor by absence of acidic excipients having large specific surface area, eg silicon dioxide**

(57) Stable pharmaceutical compositions comprising an ACE inhibitor (which are otherwise susceptible to degradation due to cyclisation, hydrolysis and oxidation) are provided. This is achieved by providing compositions substantially free of any acidic excipients having a large specific surface area, especially substantially free of colloidal silicon dioxide.
The composition also comprises one or more excipients, which are preferably compatible with the ACE inhibitor.
The ACE inhibitor is preferably perindopril or ramipril.
The composition may be used as a medicament for the treatment or prevention of a cardiovascular disorder, hypertension, coronary heart disease or a cerebrovascular disease. The composition may further comprise a β-blocker, a diuretic, a calcium-channel blocker, a vasodilator anti- hypertensive drug, or an angiotensin II receptor antagonist.

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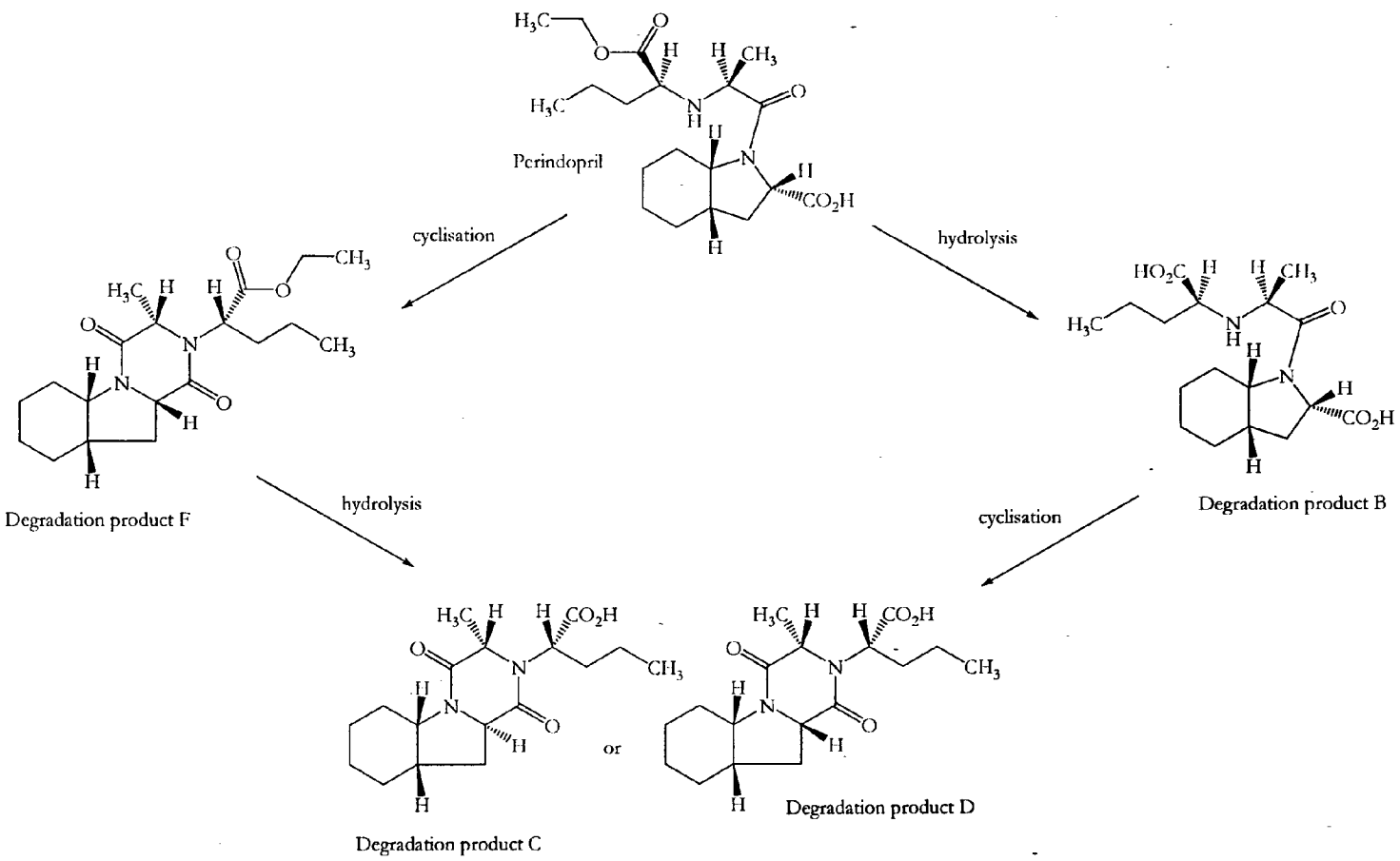
Perindopril
cyclisation
hydrolysis
Degradation product F
Degradation product B
hydrolysis
cyclisation
or
Degradation product C
Degradation product D

Figure 1

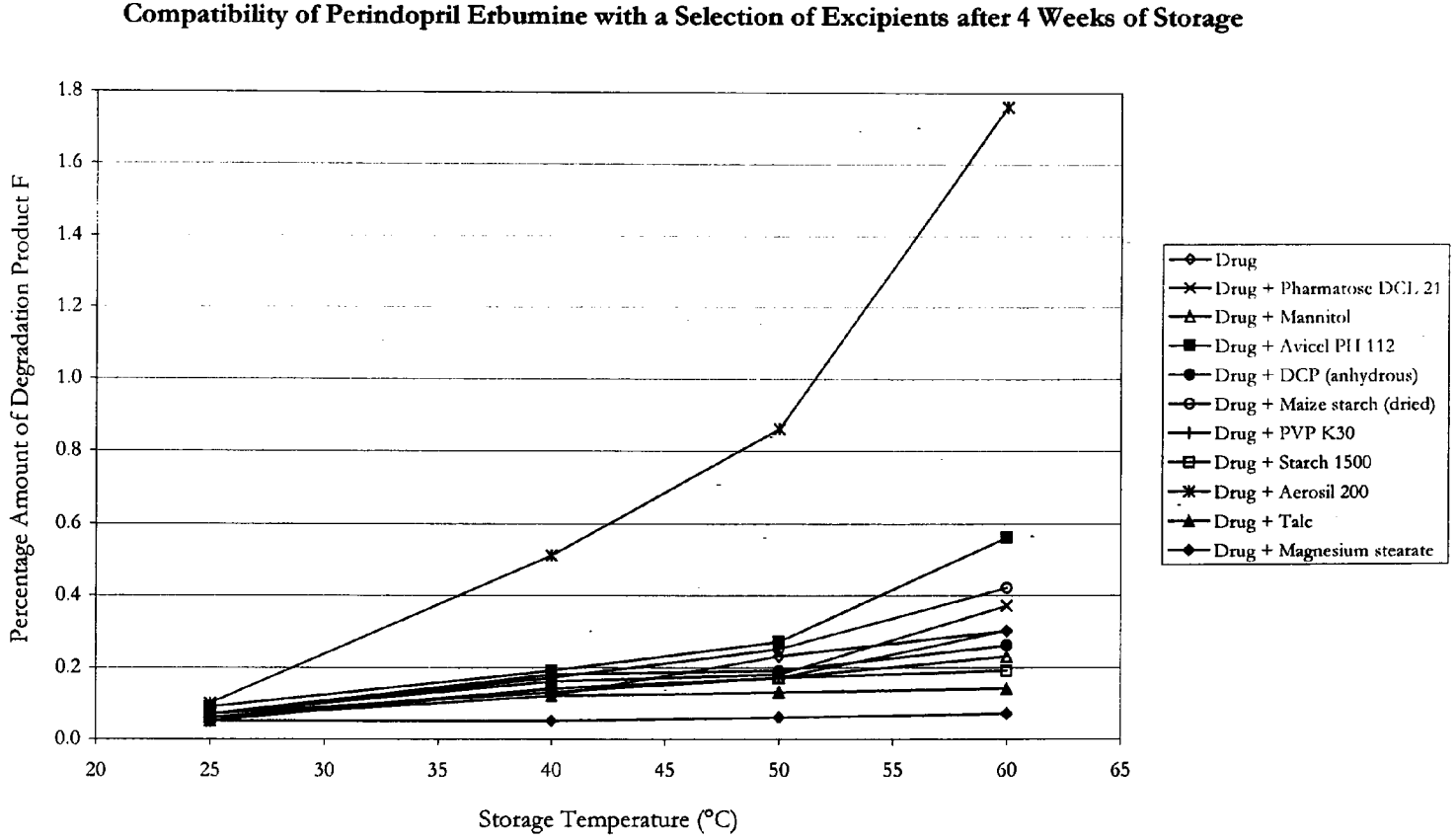
Compatibility of Perindopril Erbumine with a Selection of Excipients after 4 Weeks of Storage
Percentage Amount of Degradation Product F
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
20
25
30
35
40
45
50
55
60
65
Storage Temperature (°C)
Drug
Drug + Pharmatose DCL 21
Drug + Mannitol
Drug + Avicel PH 112
Drug + DCP (anhydrous)
Drug + Maize starch (dried)
Drug + PVP K30
Drug + Starch 1500
Drug + Aerosil 200
Drug + Talc
Drug + Magnesium stearate

Figure 2

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Pharmaceutical Composition

Technical field

The present invention relates to a stable pharmaceutical composition comprising an ACE inhibitor. In particular, the invention relates to a composition, which comprises one or more excipients, which are compatible with the ACE inhibitor. More specifically, the composition is substantially free of colloidal silicon dioxide. The composition may be for the use as a medicament for the treatment of a cardiovascular disorder, hypertension, coronary heart disease or a cerebrovascular disease.

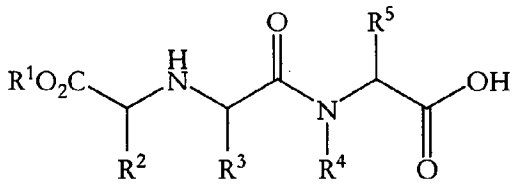
The present invention further relates to a method of preparing the pharmaceutical composition, a method of providing a stable pharmaceutical composition by providing the composition substantially free of colloidal silicon dioxide, and a use of a substantial absence of colloidal silicon dioxide to provide a stable pharmaceutical composition.

Background art

ACE inhibitors, i.e. inhibitors of angiotensin converting enzymes, are drugs useful in the treatment of cardiovascular disorders, in particular hypertension and coronary heart disease. It has been widely observed that ACE inhibitors are susceptible to degradation between the time of manufacture and the time of desired usage, in particular due to cyclization, hydrolysis and oxidation. Typical degradation products are hydrolytic degradation products formed by hydrolysis of the ACE inhibitor and diketopiperazine degradation products formed by cyclization of the ACE inhibitor.

Most, if not all, known ACE inhibitors have ester (CO-O), amide (CO-N), thio-ester (CO-S) and/or phospho-ester (PO-O) bonds. Such bonds are susceptible to hydrolysis leading to the formation of hydrolytic degradation products.

Moreover, many known ACE inhibitors are of formula **1**



1

wherein

R^1 is H or C_1-C_3 alkyl,

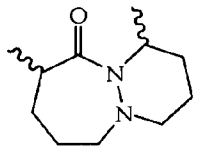
R^2 is C_1-C_3 alkyl optionally substituted with phenyl,

R^3 is C_1-C_5 alkyl optionally substituted with $-NH_2$, or together with R^4 forms an ε-caprolactam derivative optionally containing a sulphur atom and/or a double bond and optionally substituted with -CH=CH-CH=CH- or $-C_4H_3S$,

R^4 is indanyl, or together with R^3 forms an ε-caprolactam derivative as defined above, or together with R^5 forms a pyrrolidine or piperidine derivative optionally containing another nitrogen atom and/or a double bond and optionally substituted with $-SCH_2CH_2S-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2-$, -CH=CH-CH=CH-, $-CH=C(OCH_3)-C(OCH_3)=CH-$, =O or $-CH_3$, and

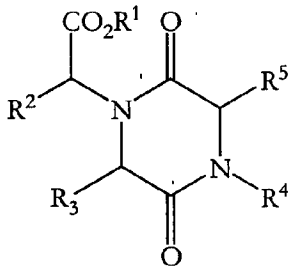
R^5 is H, or together with R^4 forms a pyrrolidine or piperidine derivative as defined above,

or wherein R^3, R^4 and R^5 together form a bicyclic ring system



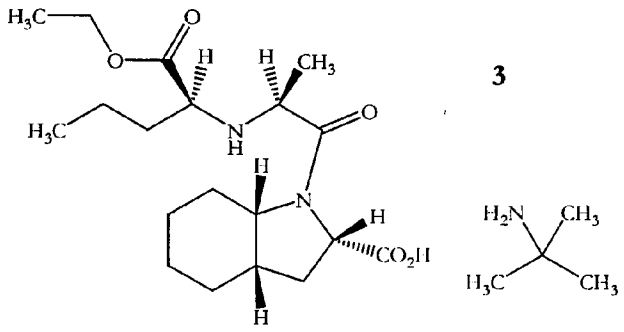
Known ACE inhibitors of formula **1** are, for example, benazepril, cilazapril, delapril, enalapril, enalaprilat, imidapril, lisinopril, moexipril, perindopril, quinapril, ramipril, spirapril, temocapril and trandolapril.

Due to their molecular structure, compounds of formula **1** are susceptible to cyclization to form the diketopiperazine degradation product of formula **2**



2

One example of an ACE inhibitor of formula **1** is perindopril erbumine, also called perindopril tert-butylamine or (2S,3aS,7aS)-1-[(S)-N-[(S)-1-(ethoxycarbonyl)butyl] alanyl]octahydro-1H-indole-2-carboxylic acid tert-butylamine salt. Perindopril erbumine is of formula **3**



3

Perindopril erbumine is a long-acting ACE inhibitor and currently used in the treatment of hypertension, coronary heart disease and cerebrovascular disease. Commercially available formulations of perindopril erbumine are currently sold under the trade names Coversyl®, Coversum®, Aceon® and Procaptan®. All of these formulations contain perindopril erbumine as active ingredient as well as lactose, microcrystalline cellulose, colloidal silicon dioxide and magnesium stearate as inactive ingredients. Known degradation products of perindopril erbumine are shown in Figure 1, including hydrolytic degradation product B, and diketopiperazine degradation products C, D and F.

Degradation of ACE inhibitors has been found to occur both in solid and in liquid states. As the degradation of an ACE inhibitor in a pharmaceutical composition increases, the concentration of available, functional ACE inhibitor decreases. Thus the shelf-life of pharmaceutical compositions comprising ACE inhibitors is limited due to this degradation. Accordingly, degradation should be avoided.

Various ways to minimize the degradation of ACE inhibitors in pharmaceutical compositions have been advocated. For example, it has been suggested that alkali or alkaline earth metal salts can stabilize ACE inhibitors in pharmaceutical compositions.

WO 01/15724 and US-6,555,551 disclose a method of stabilizing pharmaceutical compositions comprising ACE inhibitors. The method comprises the step of mixing an alcoholic dispersion of an ACE inhibitor with an aqueous solution or dispersion of a metal compound; the resulting mixture may be dried. Suitable metal compounds are alkali or alkaline earth metal salts.

EP-0,280,999 and US-4,743,450 teach that the cyclization, hydrolysis and discolouration of pharmaceutical compositions comprising ACE inhibitors are minimized by formulating the compositions with a metal-containing alkaline stabilizer. The metal-containing alkaline stabilizer is preferably an inorganic salt of an alkali or alkaline earth metal, such as magnesium, calcium or sodium borate, silicate or carbonate.

WO 99/62560 and US-6,417,196 disclose pharmaceutical compositions comprising ACE inhibitors, which are stabilized by the presence of magnesium oxide, preferably in combination with a hydrolysis-minimizing agent. The presence of magnesium oxide is also said to lend itself to favourable processing conditions during the manufacture of the ACE inhibitor-containing compositions, especially processing by wet granulation.

EP-0,545,194, US-5,350,582, US-5,690,962, WO 97/05881 and US-5,573,780 propose stabilizing enalapril maleate, an ACE inhibitor, by converting it into its sodium salt.

It has also been suggested that certain acids can be used to stabilize ACE inhibitors in pharmaceutical compositions. EP-0,468,929, US-6,300,361 and US-6,300,362 disclose the use of hydrochloric acid donors as stabilizers in pharmaceutical compositions comprising ACE inhibitors. Suitable hydrochloric acid donors are amino acid hydrochlorides, such as glycine, glutamic acid, betaine, alanine, valine, lysine, arginine and aspartic acid hydrochloride, and Lewis acid chlorides, such as ferric, zinc and aluminium chloride.

EP-0,264,888 and US-4,793,998 suggest that the cyclization, hydrolysis and oxidative discolouration of ACE inhibitors in pharmaceutical compositions can be minimized by formulating them with ascorbic acid as stabilizer, optionally in combination with fumaric, citric and/or maleic acid.

Moreover, the use of protective coatings has been advocated to stabilize ACE inhibitors in pharmaceutical compositions. EP-0,317,878, US-5,151,433 and US-5,442,008 disclose pharmaceutical compositions comprising ACE inhibitors, in which the ACE inhibitors are stabilized by a polymeric protective coating and/or by a buffer which maintains the pH of the compositions between 5.5 and 8.0.

WO 95/34283, EP-0,624,364 and US-5,527,540 disclose pharmaceutical compositions comprising an alkali-sensitive active substance, such as an ACE inhibitor, and an effervescent system, such as a carbonate component. To stabilise the active substance, it is embedded in at least one of the following compounds: an edible organic acid, a higher alcohol, a hydrocolloid, a long-chain polyvinyl pyrrolidone, and is preferably coated with at least one of said compounds. The carbonate component is also preferably embedded in at least one edible organic acid and coated by the same or another acid.

It has still further been suggested to stabilize ACE inhibitors in pharmaceutical compositions by derivatisation. For example, WO 02/03970 discloses a transdermal therapeutic system comprising an adhesive matrix. The matrix comprises an ACE inhibitor derivative, which has been stabilized by derivatisation into a salt or di-ester.

Finally an incompatibility between ACE inhibitors and certain excipients has been observed in US-5,562,921. US-5,562,921 discloses that enalapril maleate is unstable when associated with many excipients commonly used in the manufacture of pharmaceutical compositions, and teaches stable pharmaceutical compositions comprising enalapril maleate, a carrier that is comprised primarily of water-soluble carbohydrates, and a lubricant other than magnesium stearate.

Despite these efforts to stabilize ACE inhibitors, there remains a long-standing need for stable pharmaceutical compositions comprising ACE inhibitors and methods of preparing the same.

Surprisingly, it has now been found that the presence of colloidal silicon dioxide promotes the degradation of ACE inhibitors in pharmaceutical compositions. This is the more surprising, because in a number of prior publications the use of colloidal silicon dioxide is advocated for use in stable pharmaceutical compositions comprising ACE inhibitors; see for example EP-0,468,929, US-6,300,361 and US-6,300,361 (examples 2A-2D, 5A, 5B, 5D and 8A-8D), WO 99/62560 (page 10, line 30), US-6,417,196 (column 6, line 55), WO 01/15724 and US-6,555,551 (formulations I, II and V) and WO 02/03970 (examples 1 to 6). Moreover, at least some of the currently commercially available compositions of perindopril erbumine contain colloidal silicon dioxide as inactive ingredient. This highlights the fact that the incompatibility between colloidal silicon dioxide and ACE inhibitors has not been recognised until now.

Summary of the invention

For the purposes of the present invention, a pharmaceutical composition comprising an ACE inhibitor is considered to be "stable", if the ACE inhibitor degrades less or more slowly than it does in known pharmaceutical compositions.

An excipient is considered to be "incompatible" with an ACE inhibitor, if it promotes the degradation of the ACE inhibitor, i.e. if the ACE inhibitor degrades more or faster in the presence of the excipient when compared to the degradation of the ACE inhibitor on its own. The terms "incompatibility", "compatible" and "compatibility" are defined accordingly.

A composition is "substantially free of colloidal silicon dioxide", if it contains less colloidal silicon dioxide than is required to cause substantial degradation of the ACE inhibitor. Preferably a composition, which is substantially free of colloidal silicon dioxide, comprises less than 0.3% by weight colloidal silicon dioxide, more preferably 0.1% by weight. The term "substantially free of any acidic excipients" is defined accordingly. Hence a composition, which is substantially free of any acidic excipients, preferably comprises less than 0.3% by weight of any acidic excipients, more preferably 0.1% by weight.

An "acidic excipient" is an excipient with a pH of 5.5 or less, or even 3.5 or less.

An "excipient having a large specific surface area" is an excipient having a specific surface area of $200m^2/g$ or more, or even $400m^2/g$ or more, when measured on a Stroehlein apparatus, single point. Alternatively, an "excipient having a large specific surface area" is an excipient having a specific surface area of $50m^2/g$ or more, or even $380m^2/g$ or more, when measured using the BET method (S. Brunauer, P. Emmett and E. Teller, "Adsorption of gases in multimolecular layers", *J. Am. Chem. Soc.*, vol. 60, pages 309-319).

A first embodiment of the present invention provides a stable pharmaceutical composition comprising an ACE inhibitor.

Preferably the composition further comprises one or more excipients, which are compatible with the ACE inhibitor. The composition may comprise two such excipients. The composition may comprise three such excipients. The composition may comprise four such excipients. The composition may comprise five such excipients. The composition may comprise six such excipients. Alternatively the composition may comprise seven or more such excipients.

The one or more excipients may be selected from carbonates (such as calcium carbonate, sodium carbonate or magnesium carbonate), phosphates (such as anhydrous dibasic calcium phosphate, dibasic calcium phosphate dihydrate, tribasic calcium phosphate or sodium phosphate), sulfates (such as calcium sulfate), silicates (such as kaolin, talc, magnesium aluminium silicate, magnesium silicate or magnesium trisilicate), carbohydrates (such as dextrates, dextrin, maltodextrin, dextrose, polydextrose, fructose, sucrose, sugar spheres, compressible sugar, confectioner's sugar, maltose, mannitol, lactose, lactitol, maltitol, sorbitol, sodium alginate, alginic acid or liquid glucose), starches (such as starch, pregelatinized starch, maize starch, corn starch or sodium starch glycolate), celluloses (such as carboxymethylcellulose calcium, carboxymethylcellulose sodium, cross-linked carboxymethylcellulose sodium, microcrystalline cellulose, silicified microcrystalline cellulose, powdered cellulose, cellulose acetate, cellulose acetate phthalate, methylcellulose, ethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose or hydroxypropyl methylcellulose), polyvinylpyrrolidones (such as povidone or crospovidone), fatty acids or fatty acid derivatives (such as hydrogenated vegetable oil, hydrogenated castor oil, mineral oil, light mineral oil, hydrogenated vegetable oil, cottonseed oil, a medium-chain triglyceride, glyceryl palmitostearate, calcium stearate, stearic acid, glyceryl monostearate, magnesium stearate, polyoxyethylene stearate, zinc stearate, sodium stearyl fumarate or glyceryl behenate), gums (such as tragacanth gum, guar gum or acacia), magnesium oxide, sodium chloride, polymethacrylate, polacrilin potassium, sodium lauryl sulfate, a poloxamer, polyethylene glycol, sodium benzoate, a carbomer, ceratonia, gelatin, polyethylene oxide, zein, and mixtures thereof. Preferably, the one or more excipients are selected from phosphates (preferably

anhydrous dibasic calcium phosphate, dibasic calcium phosphate dihydrate or tribasic calcium phosphate), silicates (preferably kaolin, talc, magnesium aluminium silicate, magnesium silicate or magnesium trisilicate), carbohydrates (preferably dextrates, maltodextrin, dextrose, polydextrose, fructose, sucrose, sugar spheres, compressible sugar, confectioner's sugar, maltose, mannitol, lactose, lactitol, maltitol, sorbitol or sodium alginate), starches (preferably starch, pregelatinized starch, maize starch, corn starch or sodium starch glycolate), celluloses (preferably carboxymethylcellulose calcium, carboxymethylcellulose sodium, cross-linked carboxymethylcellulose sodium, microcrystalline cellulose, powdered cellulose, cellulose acetate, cellulose acetate phthalate, methylcellulose, ethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose or hydroxypropyl methylcellulose), polyvinylpyrrolidones (preferably povidone or crospovidone), fatty acids or fatty acid derivatives (preferably hydrogenated vegetable oil, glyceryl palmitostearate, calcium stearate, stearic acid, glyceryl monostearate, magnesium stearate, zinc stearate, sodium stearyl fumarate or glyceryl behenate), gums (preferably guar gum), sodium chloride, polymethacrylate, sodium lauryl sulfate, a poloxamer, polyethylene glycol, sodium benzoate, a carbomer, ceratonia, polyethylene oxide, zein, and mixtures thereof. Preferably the one or more excipients are selected from lactose, microcrystalline cellulose, mannitol, dibasic calcium phosphate, maize starch, pregelatinised starch, polyvinylpyrrolidone, talc and magnesium stearate.

Preferably the composition further comprises a glidant, which is substantially free of colloidal silicon dioxide. Preferably the composition is substantially free of colloidal silicon dioxide.

A further embodiment of the present invention provides a pharmaceutical composition comprising an ACE inhibitor, wherein the composition is substantially free of any acidic excipients having a large specific surface area. Preferably the composition is stable.

A further embodiment of the present invention provides a pharmaceutical composition comprising an ACE inhibitor, a diluent, a disintegrant, a glidant and a

lubricant, wherein the diluent, disintegrant, glidant and lubricant are compatible with the ACE inhibitor, and wherein the composition is substantially free of colloidal silicon dioxide. The present invention also provides a pharmaceutical composition comprising an ACE inhibitor, a diluent, a disintegrant, a glidant and a lubricant, wherein the diluent, disintegrant, glidant and lubricant are compatible with the ACE inhibitor, and wherein the composition is substantially free of any acidic excipients having a large specific surface area.

The diluent may be a carbonate (such as calcium carbonate, sodium carbonate or magnesium carbonate), a phosphate (such as anhydrous dibasic calcium phosphate, dibasic calcium phosphate dihydrate, tribasic calcium phosphate or sodium phosphate), a sulfate (such as calcium sulfate), a silicate (such as kaolin or talc), a carbohydrate (such as dextrates, dextrin, maltodextrin, dextrose, fructose, sucrose, sugar spheres, compressible sugar, confectioner's sugar, maltose, mannitol, lactose, lactitol, maltitol, sorbitol or sodium alginate), a starch (such as starch, pregelatinized starch or maize starch), a cellulose (such as carboxymethylcellulose calcium, cellulose acetate, microcrystalline cellulose, silicified microcrystalline cellulose or powdered cellulose), a polyvinylpyrrolidone (such as povidone), a fatty acid or fatty acid derivative (such as hydrogenated vegetable oil or glyceryl palmitostearate), a gum (such as tragacanth gum), magnesium oxide, sodium chloride, polymethacrylate, or a mixture thereof. Preferably the diluent is a phosphate (preferably anhydrous dibasic calcium phosphate, dibasic calcium phosphate dihydrate or tribasic calcium phosphate), a silicate (preferably kaolin or talc), a carbohydrate (preferably dextrates, maltodextrin, dextrose, fructose, sucrose, sugar spheres, compressible sugar, confectioner's sugar, maltose, mannitol, lactose, lactitol, maltitol, sorbitol or sodium alginate), a starch (preferably starch, pregelatinized starch or maize starch), a cellulose (preferably carboxymethylcellulose calcium, cellulose acetate, microcrystalline cellulose or powdered cellulose), a polyvinylpyrrolidone (preferably povidone), a fatty acid or fatty acid derivative (preferably hydrogenated vegetable oil or glyceryl palmitostearate), sodium chloride, polymethacrylate, or a mixture thereof. Preferably the diluent is a cellulose, a carbohydrate, a phosphate or talc. If present, preferably the cellulose is

microcrystalline cellulose. If present, preferably the carbohydrate is lactose or mannitol. If present, preferably the phosphate is dibasic calcium phosphate.

The disintegrant may be a silicate (such as magnesium aluminium silicate), a carbohydrate (such as sodium alginate or alginic acid), a starch (such as starch, pregelatinized starch, maize starch, corn starch or sodium starch glycolate), a cellulose (such as carboxymethylcellulose calcium, cross-linked carboxymethylcellulose sodium, carboxymethylcellulose sodium, microcrystalline cellulose, powdered cellulose, low-substituted hydroxypropyl cellulose or methylcellulose), a polyvinylpyrrolidone (such as povidone or crospovidone), a gum (such as guar gum), polacrilin potassium, or a mixture thereof. Preferably the disintegrant is a silicate (preferably magnesium aluminium silicate), a carbohydrate (preferably sodium alginate), a starch (preferably starch, pregelatinized starch, maize starch, corn starch or sodium starch glycolate), a cellulose (preferably carboxymethylcellulose calcium, cross-linked carboxymethylcellulose sodium, carboxymethylcellulose sodium, microcrystalline cellulose, powdered cellulose, low-substituted hydroxypropyl cellulose or methylcellulose), a polyvinylpyrrolidone (preferably povidone or crospovidone), a gum (preferably guar gum), or a mixture thereof. Preferably the disintegrant is a starch. If present, preferably the starch is maize starch or pregelatinised starch.

The glidant may be a phosphate (such as tribasic calcium phosphate), a silicate (such as magnesium silicate, magnesium trisilicate or talc), a starch (such as starch, pregelatinized starch or maize starch), a cellulose (such as powdered cellulose), a fatty acid or fatty acid derivative (such as calcium stearate), or a mixture thereof. Preferably the glidant is tribasic calcium phosphate, magnesium silicate, magnesium trisilicate, talc, pregelatinized starch, maize starch, powdered cellulose, calcium stearate, or a mixture thereof. Preferably the glidant is a starch or talc. If present, preferably the starch is maize starch or pregelatinised starch.

The lubricant may be a silicate (such as talc), a cellulose (such as microcrystalline cellulose), a fatty acid or fatty acid derivative (such as hydrogenated castor oil, mineral oil, light mineral oil, hydrogenated vegetable oil, stearic acid, calcium

stearate, glyceryl monostearate, glyceryl palmitostearate, magnesium stearate, polyoxyethylene stearate, zinc stearate, sodium stearyl fumarate, glyceryl behenate or a medium-chain triglyceride), sodium lauryl sulfate, a poloxamer, polyethylene glycol, sodium benzoate, sodium chloride, or a mixture thereof. Preferably the lubricant is a silicate (preferably talc), a cellulose (preferably microcrystalline cellulose), a fatty acid or fatty acid derivative (preferably hydrogenated vegetable oil, stearic acid, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, magnesium stearate, zinc stearate, sodium stearyl fumarate or glyceryl behenate), sodium lauryl sulfate, a poloxamer, polyethylene glycol, sodium benzoate, sodium chloride, or a mixture thereof. Preferably the lubricant is an alkali or earth alkaline metal salt of a saturated C_{16-24} carboxylic acid. If present, preferably the carboxylic acid salt is magnesium stearate.

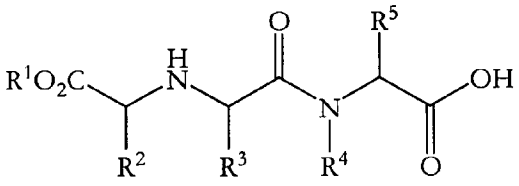
Preferably the composition further comprises a binder. The binder may be a silicate (such as magnesium aluminium silicate), a carbohydrate (such as dextrates, dextrin, maltodextrin, dextrose, polydextrose, liquid glucose, sucrose, compressible sugar, confectioner's sugar, sorbitol, sodium alginate or alginic acid), a starch (such as starch, pregelatinized starch or maize starch), a cellulose (such as carboxymethylcellulose calcium, carboxymethylcellulose sodium, cellulose acetate phthalate, microcrystalline cellulose, powdered cellulose, methylcellulose, ethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose or hydroxypropyl methylcellulose), a polyvinylpyrrolidone (such as povidone), a fatty acid or fatty acid derivative (such as cottonseed oil, hydrogenated vegetable oil, stearic acid or glyceryl behenate), a gum (such as guar gum or acacia), polymethacrylate, a carbomer, a poloxamer, ceratonia, gelatin, polyethylene oxide, zein, or a mixture thereof. If present, preferably the binder is a silicate (preferably magnesium aluminium silicate), a carbohydrate (preferably dextrates, maltodextrin, dextrose, polydextrose, sucrose, compressible sugar, confectioner's sugar, sorbitol or sodium alginate), a starch (preferably starch, pregelatinized starch or maize starch), a cellulose (preferably carboxymethylcellulose calcium, carboxymethylcellulose sodium, cellulose acetate phthalate, microcrystalline cellulose, powdered cellulose, methylcellulose, ethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose or hydroxypropyl

methylcellulose), a polyvinylpyrrolidone (preferably povidone), a fatty acid or fatty acid derivative (preferably hydrogenated vegetable oil, stearic acid or glyceryl behenate), a gum (preferably guar gum), polymethacrylate, a carbomer, a poloxamer, ceratonia, polyethylene oxide, zein, or a mixture thereof. If present, preferably the binder is a starch or polyvinylpyrrolidone. If present, preferably the starch is maize starch or pregelatinised starch.

A further embodiment of the present invention provides a pharmaceutical composition comprising an ACE inhibitor and four or more excipients selected from lactose, microcrystalline cellulose, mannitol, dibasic calcium phosphate, maize starch, pregelatinised starch, polyvinylpyrrolidone, talc and magnesium stearate, wherein the composition is substantially free of colloidal silicon dioxide.

The composition may comprise five excipients selected from lactose, microcrystalline cellulose, mannitol, dibasic calcium phosphate, maize starch, pregelatinised starch, polyvinylpyrrolidone, talc and magnesium stearate. The composition may comprise six such excipients. Alternatively the composition may comprise seven or more such excipients.

In any of the above pharmaceutical compositions, the ACE inhibitor preferably has an ester (CO-O), amide (CO-N), thio-ester (CO-S) and/or phospho-ester (PO-O) bond. Preferably the ACE inhibitor is of formula **1**



1

wherein

R^1 is H or C_1-C_3 alkyl,

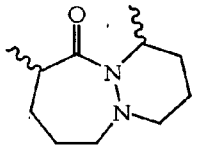
R^2 is C_1-C_3 alkyl optionally substituted with phenyl,

R^3 is C_1-C_5 alkyl optionally substituted with $-NH_2$, or together with R^4 forms an ε-caprolactam derivative optionally containing a sulphur atom and/or a double bond and optionally substituted with -CH=CH-CH=CH- or $-C_4H_3S$,

R^4 is indanyl, or together with R^3 forms an ε-caprolactam derivative as defined above, or together with R^5 forms a pyrrolidine or piperidine derivative optionally containing another nitrogen atom and/or a double bond and optionally substituted with $-SCH_2CH_2S-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH=CH-CH=CH-$, $-CH=C(OCH_3)-C(OCH_3)=CH-$, $=O$ or $-CH_3$, and

R^5 is H, or together with R^4 forms a pyrrolidine or piperidine derivative as defined above,

or wherein R^3, R^4 and R^5 together form a bicyclic ring system



The ACE inhibitor may be alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, libenzapril, lisinopril, moexipril, moveltipril, pentopril, perindopril, quinapril, ramipril, rentiapril, spirapril, sosinopril, temocapril, trandolapril or zofenopril, or a pharmaceutically acceptable salt or derivative thereof.

The ACE inhibitor may be alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, fosinopril, imidapril, libenzapril, lisinopril, moexipril, moveltipril, pentopril, perindopril, quinapril, ramipril, rentiapril, spirapril, sosinopril, temocapril, trandolapril or zofenopril, or a pharmaceutically acceptable salt or derivative thereof.

The ACE inhibitor may be benazepril, cilazapril, delapril, fosinopril, imidapril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril or zofenopril, or a pharmaceutically acceptable salt or derivative thereof. The ACE inhibitor may be benazepril, cilazapril, delapril, fosinopril, imidapril, moexipril, perindopril, ramipril, spirapril, trandolapril or zofenopril, or a pharmaceutically acceptable salt or derivative thereof.

Optionally the ACE inhibitor is not enalapril or enalaprilat or a pharmaceutically acceptable salt or derivative thereof. Optionally the ACE inhibitor is not lisinopril or a pharmaceutically acceptable salt or derivative thereof. Optionally the ACE inhibitor is not quinapril or a pharmaceutically acceptable salt or derivative thereof.

Preferably the ACE inhibitor is benazepril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is cilazapril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is delapril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is fosinopril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is imidapril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is moexipril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is quinapril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is ramipril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is spirapril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is trandolapril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is zofenopril or a pharmaceutically acceptable salt or derivative thereof. More preferably the ACE inhibitor is perindopril or a pharmaceutically acceptable salt or derivative thereof. Most preferably the ACE inhibitor is perindopril erbumine.

The composition may preferably comprise:

2-8% by weight perindopril erbumine,
20-75% by weight lactose anhydrous,
15-75% by weight microcrystalline cellulose,
0-15% by weight maize starch, preferably 0.2-15% by weight,
0.5-8% by weight magnesium stearate, and
0-15% by weight talc, preferably 0.2-15% by weight.

A further embodiment of the present invention provides a pharmaceutical composition comprising an ACE inhibitor and three or more excipients selected from lactose, microcrystalline cellulose, mannitol, dibasic calcium phosphate, maize

starch, pregelatinised starch, polyvinylpyrrolidone, talc and magnesium stearate, wherein the composition is substantially free of colloidal silicon dioxide, and wherein the ACE inhibitor is alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, fosinopril, imidapril, libenzapril, lisinopril, moexipril, moveltipril, pentopril, perindopril, quinapril, ramipril, rentiapril, spirapril, sosinopril, temocapril, trandolapril or zofenopril, or a pharmaceutically acceptable salt or derivative thereof.

The composition may comprise four excipients selected from lactose, microcrystalline cellulose, mannitol, dibasic calcium phosphate, maize starch, pregelatinised starch, polyvinylpyrrolidone, talc and magnesium stearate. The composition may comprise five such excipients. The composition may comprise six such excipients. Alternatively the composition may comprise seven or more such excipients.

The ACE inhibitor may be benazepril, cilazapril, delapril, fosinopril, imidapril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril or zofenopril, or a pharmaceutically acceptable salt or derivative thereof. The ACE inhibitor may be benazepril, cilazapril, delapril, fosinopril, imidapril, moexipril, perindopril, ramipril, spirapril, trandolapril or zofenopril, or a pharmaceutically acceptable salt or derivative thereof.

Optionally the ACE inhibitor is not enalapril or enalaprilat or a pharmaceutically acceptable salt or derivative thereof. Optionally the ACE inhibitor is not lisinopril or a pharmaceutically acceptable salt or derivative thereof. Optionally the ACE inhibitor is not quinapril or a pharmaceutically acceptable salt or derivative thereof.

Preferably the ACE inhibitor is benazepril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is cilazapril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is delapril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is fosinopril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is imidapril or a pharmaceutically acceptable salt or derivative

thereof. Preferably the ACE inhibitor is moexipril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is quinapril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is ramipril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is spirapril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is trandolapril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is zofenopril or a pharmaceutically acceptable salt or derivative thereof. More preferably the ACE inhibitor is perindopril or a pharmaceutically acceptable salt or derivative thereof. Most preferably the ACE inhibitor is perindopril erbumine.

The composition may comprise:

2-8% by weight perindopril erbumine,

20-75% by weight lactose anhydrous,

15-75% by weight microcrystalline cellulose,

0-15% by weight maize starch, preferably 0.2-15% by weight,

0.5-8% by weight magnesium stearate, and

0-15% by weight talc, preferably 0.2-15% by weight.

A further embodiment of the present invention provides a stable pharmaceutical composition comprising perindopril or a pharmaceutically acceptable salt or derivative thereof, and one or more excipients compatible with perindopril or the pharmaceutically acceptable salt or derivative thereof. The present invention also provides a pharmaceutical composition comprising perindopril or a pharmaceutically acceptable salt or derivative thereof, and one or more excipients compatible with perindopril or the pharmaceutically acceptable salt or derivative thereof, wherein the composition is substantially free of colloidal silicon dioxide. The present invention also provides a pharmaceutical composition comprising perindopril or a pharmaceutically acceptable salt or derivative thereof, and one or more excipients compatible with perindopril or the pharmaceutically acceptable salt or derivative thereof, wherein the composition is substantially free of any acidic excipients having a large specific surface area. Preferably the composition is stable.

Preferably the composition comprises perindopril erbumine.

The composition may comprise two different excipients compatible with perindopril or the pharmaceutically acceptable salt or derivative thereof. The composition may comprise three such excipients. The composition may comprise four such excipients. The composition may comprise five such excipients. Alternatively the composition may comprise six or more such excipients.

The excipient or excipients may be a carbonate (such as calcium carbonate, sodium carbonate or magnesium carbonate), a phosphate (such as anhydrous dibasic calcium phosphate, dibasic calcium phosphate dihydrate, tribasic calcium phosphate or sodium phosphate), a sulfate (such as calcium sulfate), a silicate (such as kaolin, talc, magnesium aluminium silicate, magnesium silicate or magnesium trisilicate), a carbohydrate (such as dextrates, dextrin, maltodextrin, dextrose, polydextrose, fructose, sucrose, sugar spheres, compressible sugar, confectioner's sugar, maltose, mannitol, lactose, lactitol, maltitol, sorbitol, sodium alginate, alginic acid or liquid glucose), a starch (such as starch, pregelatinized starch, maize starch, corn starch or sodium starch glycolate), a cellulose (such as carboxymethylcellulose calcium, carboxymethylcellulose sodium, cross-linked carboxymethylcellulose sodium, microcrystalline cellulose, silicified microcrystalline cellulose, powdered cellulose, cellulose acetate, cellulose acetate phthalate, methylcellulose, ethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose or hydroxypropyl methylcellulose), a polyvinylpyrrolidone (such as povidone or crospovidone), a fatty acid or fatty acid derivative (such as hydrogenated vegetable oil, hydrogenated castor oil, mineral oil, light mineral oil, hydrogenated vegetable oil, cottonseed oil, a medium-chain triglyceride, glyceryl palmitostearate, calcium stearate, stearic acid, glyceryl monostearate, magnesium stearate, polyoxyethylene stearate, zinc stearate, sodium stearyl fumarate or glyceryl behenate), a gum (such as tragacanth gum, guar gum or acacia), magnesium oxide, sodium chloride, polymethacrylate, polacrilin potassium, sodium lauryl sulfate, a poloxamer, polyethylene glycol, sodium benzoate, a carbomer, ceratonia, gelatin, polyethylene oxide, zein, or a mixture thereof. Preferably, the excipient or excipients are selected from phosphates (preferably anhydrous dibasic calcium

phosphate, dibasic calcium phosphate dihydrate or tribasic calcium phosphate), silicates (preferably kaolin, talc, magnesium aluminium silicate, magnesium silicate or magnesium trisilicate), carbohydrates (preferably dextrates, maltodextrin, dextrose, polydextrose, fructose, sucrose, sugar spheres, compressible sugar, confectioner's sugar, maltose, mannitol, lactose, lactitol, maltitol, sorbitol or sodium alginate), starches (preferably starch, pregelatinized starch, maize starch, corn starch or sodium starch glycolate), celluloses (preferably carboxymethylcellulose calcium, carboxymethylcellulose sodium, cross-linked carboxymethylcellulose sodium, microcrystalline cellulose, powdered cellulose, cellulose acetate, cellulose acetate phthalate, methylcellulose, ethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose or hydroxypropyl methylcellulose), polyvinylpyrrolidones (preferably povidone or crospovidone), fatty acids or fatty acid derivatives (preferably hydrogenated vegetable oil, glyceryl palmitostearate, calcium stearate, stearic acid, glyceryl monostearate, magnesium stearate, zinc stearate, sodium stearyl fumarate or glyceryl behenate), gums (preferably guar gum), sodium chloride, polymethacrylate, sodium lauryl sulfate, a poloxamer, polyethylene glycol, sodium benzoate, a carbomer, ceratonia, polyethylene oxide, zein, or a mixture thereof. Preferably the excipient or excipients are selected from lactose, microcrystalline cellulose, mannitol, dibasic calcium phosphate, maize starch, pregelatinised starch, polyvinylpyrrolidone, talc and magnesium stearate.

A further embodiment of the present invention provides a stable pharmaceutical composition comprising ramipril or a pharmaceutically acceptable salt or derivative thereof, and one or more excipients compatible with ramipril or the pharmaceutically acceptable salt or derivative thereof. The present invention also provides a pharmaceutical composition comprising ramipril or a pharmaceutically acceptable salt or derivative thereof, and one or more excipients compatible with ramipril or the pharmaceutically acceptable salt or derivative thereof, wherein the composition is substantially free of colloidal silicon dioxide. The present invention also provides a pharmaceutical composition comprising ramipril or a pharmaceutically acceptable salt or derivative thereof, and one or more excipients compatible with ramipril or the pharmaceutically acceptable salt or derivative

thereof, wherein the composition is substantially free of any acidic excipients having a large specific surface area. Preferably the composition is stable.

Preferably the composition comprises ramipril.

The composition may comprise two different excipients compatible with ramipril or the pharmaceutically acceptable salt or derivative thereof. The composition may comprise three such excipients. The composition may comprise four such excipients. The composition may comprise five such excipients. Alternatively the composition may comprise six or more such excipients.

The excipient or excipients may be a carbonate (such as calcium carbonate, sodium carbonate or magnesium carbonate), a phosphate (such as anhydrous dibasic calcium phosphate, dibasic calcium phosphate dihydrate, tribasic calcium phosphate or sodium phosphate), a sulfate (such as calcium sulfate), a silicate (such as kaolin, talc, magnesium aluminium silicate, magnesium silicate or magnesium trisilicate), a carbohydrate (such as dextrates, dextrin, maltodextrin, dextrose, polydextrose, fructose, sucrose, sugar spheres, compressible sugar, confectioner's sugar, maltose, mannitol, lactose, lactitol, maltitol, sorbitol, sodium alginate, alginic acid or liquid glucose), a starch (such as starch, pregelatinized starch, maize starch, corn starch or sodium starch glycolate), a cellulose (such as carboxymethylcellulose calcium, carboxymethylcellulose sodium, cross-linked carboxymethylcellulose sodium, microcrystalline cellulose, silicified microcrystalline cellulose, powdered cellulose, cellulose acetate, cellulose acetate phthalate, methylcellulose, ethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose or hydroxypropyl methylcellulose), a polyvinylpyrrolidone (such as povidone or crospovidone), a fatty acid or fatty acid derivative (such as hydrogenated vegetable oil, hydrogenated castor oil, mineral oil, light mineral oil, hydrogenated vegetable oil, cottonseed oil, a medium-chain triglyceride, glyceryl palmitostearate, calcium stearate, stearic acid, glyceryl monostearate, magnesium stearate, polyoxyethylene stearate, zinc stearate, sodium stearyl fumarate or glyceryl behenate), a gum (such as tragacanth gum, guar gum or acacia), magnesium oxide, sodium chloride, polymethacrylate, polacrilin potassium, sodium lauryl sulfate, a

poloxamer, polyethylene glycol, sodium benzoate, a carbomer, ceratonia, gelatin, polyethylene oxide, zein, or a mixture thereof. Preferably, the excipient or excipients are selected from phosphates (preferably anhydrous dibasic calcium phosphate, dibasic calcium phosphate dihydrate or tribasic calcium phosphate), silicates (preferably kaolin, talc, magnesium aluminium silicate, magnesium silicate or magnesium trisilicate), carbohydrates (preferably dextrates, maltodextrin, dextrose, polydextrose, fructose, sucrose, sugar spheres, compressible sugar, confectioner's sugar, maltose, mannitol, lactose, lactitol, maltitol, sorbitol or sodium alginate), starches (preferably starch, pregelatinized starch, maize starch, corn starch or sodium starch glycolate), celluloses (preferably carboxymethylcellulose calcium, carboxymethylcellulose sodium, cross-linked carboxymethylcellulose sodium, microcrystalline cellulose, powdered cellulose, cellulose acetate, cellulose acetate phthalate, methylcellulose, ethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose or hydroxypropyl methylcellulose), polyvinylpyrrolidones (preferably povidone or crospovidone), fatty acids or fatty acid derivatives (preferably hydrogenated vegetable oil, glyceryl palmitostearate, calcium stearate, stearic acid, glyceryl monostearate, magnesium stearate, zinc stearate, sodium stearyl fumarate or glyceryl behenate), gums (preferably guar gum), sodium chloride, polymethacrylate, sodium lauryl sulfate, a poloxamer, polyethylene glycol, sodium benzoate, a carbomer, ceratonia, polyethylene oxide, zein, or a mixture thereof. Preferably the excipient or excipients are selected from lactose, microcrystalline cellulose, mannitol, dibasic calcium phosphate, maize starch, pregelatinised starch, polyvinylpyrrolidone, talc, magnesium stearate, glycerol dibehenate, sodium starch glycolate and sodium stearyl fumarate. Preferably the composition comprises glycerol dibehenate.

All of the compositions of the present invention are preferably stable.

All of the compositions of the present invention may optionally further comprise a β-blocker, a diuretic, a calcium-channel blocker, a vasodilator anti-hypertensive drug, or an angiotensin II receptor antagonist.

Typically, the compositions of the present invention are suitable for oral, parental, transdermal, airway, rectal, vaginal or topical administration. Preferably the compositions are suitable for oral administration.

Compositions suitable for oral administration are typically provided in the form of tablets, capsules, caplets, troches, lozenges, powder or granules. The compositions may be in unit dosage form comprising 2-20mg of the ACE inhibitor.

Preferably, compositions suitable for oral administration are provided in the form of tablets. If desired, the tablets may be coated with a material, such as glyceryl monostearate, glyceryl distearate or glycerol dibehenate. The tablets may comprise excipients such as carbonates (such as calcium carbonate, sodium carbonate or magnesium carbonate), phosphates (such as anhydrous dibasic calcium phosphate, dibasic calcium phosphate dihydrate, tribasic calcium phosphate or sodium phosphate), sulfates (such as calcium sulfate), silicates (such as kaolin, talc, magnesium aluminium silicate, magnesium silicate or magnesium trisilicate), carbohydrates (such as dextrates, dextrin, maltodextrin, dextrose, polydextrose, fructose, sucrose, sugar spheres, compressible sugar, confectioner's sugar, maltose, mannitol, lactose, lactitol, maltitol, sorbitol, sodium alginate, alginic acid or liquid glucose), starches (such as starch, pregelatinized starch, maize starch, corn starch or sodium starch glycolate), celluloses (such as carboxymethylcellulose calcium, carboxymethylcellulose sodium, cross-linked carboxymethylcellulose sodium, microcrystalline cellulose, silicified microcrystalline cellulose, powdered cellulose, cellulose acetate, cellulose acetate phthalate, methylcellulose, ethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose or hydroxypropyl methylcellulose), polyvinylpyrrolidones (such as povidone or crospovidone), fatty acids or fatty acid derivatives (such as hydrogenated vegetable oil, hydrogenated castor oil, mineral oil, light mineral oil, hydrogenated vegetable oil, cottonseed oil, a medium-chain triglyceride, glyceryl palmitostearate, calcium stearate, stearic acid, glyceryl monostearate, magnesium stearate, polyoxyethylene stearate, zinc stearate, sodium stearyl fumarate or glyceryl behenate), gums (such as tragacanth gum, guar gum or acacia), magnesium oxide, sodium chloride, polymethacrylate, polacrilin potassium, sodium lauryl sulfate, a

poloxamer, polyethylene glycol, sodium benzoate, a carbomer, ceratonia, gelatin, polyethylene oxide, zein, or a mixture thereof. Preferably, the tablets comprise excipients such as phosphates (preferably anhydrous dibasic calcium phosphate, dibasic calcium phosphate dihydrate or tribasic calcium phosphate), silicates (preferably kaolin, talc, magnesium aluminium silicate, magnesium silicate or magnesium trisilicate), carbohydrates (preferably dextrates, maltodextrin, dextrose, polydextrose, fructose, sucrose, sugar spheres, compressible sugar, confectioner's sugar, maltose, mannitol, lactose, lactitol, maltitol, sorbitol or sodium alginate), starches (preferably starch, pregelatinized starch, maize starch, corn starch or sodium starch glycolate), celluloses (preferably carboxymethylcellulose calcium, carboxymethylcellulose sodium, cross-linked carboxymethylcellulose sodium, microcrystalline cellulose, powdered cellulose, cellulose acetate, cellulose acetate phthalate, methylcellulose, ethylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose or hydroxypropyl methylcellulose), polyvinylpyrrolidones (preferably povidone or crospovidone), fatty acids or fatty acid derivatives (preferably hydrogenated vegetable oil, glyceryl palmitostearate, calcium stearate, stearic acid, glyceryl monostearate, magnesium stearate, zinc stearate, sodium stearyl fumarate or glyceryl behenate), gums (preferably guar gum), sodium chloride, polymethacrylate, sodium lauryl sulfate, a poloxamer, polyethylene glycol, sodium benzoate, a carbomer, ceratonia, polyethylene oxide, zein, or a mixture thereof.

Preferably the composition is for use as a medicament, typically for the treatment or prevention of a cardiovascular disorder, hypertension, coronary heart disease or a cerebrovascular disease.

A further embodiment of the present invention provides a method of treating or preventing a cardiovascular disorder, hypertension, coronary heart disease or a cerebrovascular disease, comprising administering an effective amount of a pharmaceutical composition of the present invention to a patient in need thereof.

A further embodiment of the present invention provides a use of a pharmaceutical composition of the present invention in the manufacture of a medicament for the

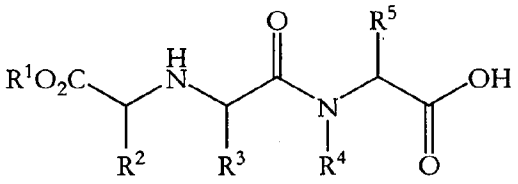
treatment or prevention of a cardiovascular disorder, hypertension, coronary heart disease or a cerebrovascular disease.

An further embodiment of the present invention provides a method of preparing a pharmaceutical composition of the present invention, comprising the step of blending the ACE inhibitor with the excipients. The composition may be prepared in batches of 5-150kg, preferably in batches of 5-50kg.

A further embodiment of the present invention provides a method of providing a stable pharmaceutical composition comprising an ACE inhibitor, the method comprising providing the composition substantially free of colloidal silicon dioxide.

Preferably the composition is stabilized to minimize the degradation of the ACE inhibitor.

Preferably the ACE inhibitor has an ester (CO-O), amide (CO-N), thio-ester (CO-S) and/or phospho-ester (PO-O) bond. Preferably the ACE inhibitor is of formula **1**



1

wherein

R^1 is H or C_1-C_3 alkyl,

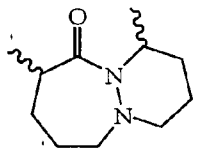
R^2 is C_1-C_3 alkyl optionally substituted with phenyl,

R^3 is C_1-C_5 alkyl optionally substituted with $-NH_2$, or together with R^4 forms an ε-caprolactam derivative optionally containing a sulphur atom and/or a double bond and optionally substituted with -CH=CH-CH=CH- or $-C_4H_3S$,

R^4 is indanyl, or together with R^3 forms an ε-caprolactam derivative as defined above, or together with R^5 forms a pyrrolidine or piperidine derivative optionally containing another nitrogen atom and/or a double bond and optionally substituted with $-SCH_2CH_2S-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2-$, -CH=CH-CH=CH-, $-CH=C(OCH_3)-C(OCH_3)=CH-$, =O or $-CH_3$, and

R^5 is H, or together with R^4 forms a pyrrolidine or piperidine derivative as defined above,

or wherein R^3, R^4 and R^5 together form a bicyclic ring system



The ACE inhibitor may be alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, libenzapril, lisinopril, moexipril, moveltipril, pentopril, perindopril, quinapril, ramipril, rentiapril, spirapril, sosinopril, temocapril, trandolapril or zofenopril, or a pharmaceutically acceptable salt or derivative thereof.

The ACE inhibitor may be alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, fosinopril, imidapril, libenzapril, lisinopril, moexipril, moveltipril, pentopril, perindopril, quinapril, ramipril, rentiapril, spirapril, sosinopril, temocapril, trandolapril or zofenopril, or a pharmaceutically acceptable salt or derivative thereof.

The ACE inhibitor may be benazepril, cilazapril, delapril, fosinopril, imidapril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril or zofenopril, or a pharmaceutically acceptable salt or derivative thereof. The ACE inhibitor may be benazepril, cilazapril, delapril, fosinopril, imidapril, moexipril, perindopril, ramipril, spirapril, trandolapril or zofenopril, or a pharmaceutically acceptable salt or derivative thereof.

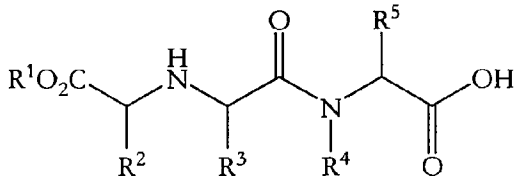
Optionally the ACE inhibitor is not enalapril or enalaprilat or a pharmaceutically acceptable salt or derivative thereof. Optionally the ACE inhibitor is not lisinopril or a pharmaceutically acceptable salt or derivative thereof. Optionally the ACE inhibitor is not quinapril or a pharmaceutically acceptable salt or derivative thereof.

Preferably the ACE inhibitor is benazepril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is cilazapril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is delapril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is fosinopril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is imidapril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is moexipril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is quinapril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is ramipril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is spirapril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is trandolapril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is zofenopril or a pharmaceutically acceptable salt or derivative thereof. More preferably the ACE inhibitor is perindopril or a pharmaceutically acceptable salt or derivative thereof. Most preferably the ACE inhibitor is perindopril erbumine.

A further embodiment of the present invention provides a use of a substantial absence of colloidal silicon dioxide to provide a stable pharmaceutical composition comprising an ACE inhibitor. The present invention also provides a use of one or more excipients to provide a stable pharmaceutical composition comprising an ACE inhibitor, wherein the composition is substantially free of colloidal silicon dioxide.

Preferably the composition is stabilized to minimize the degradation of the ACE inhibitor.

Preferably the ACE inhibitor has an ester (CO-O), amide (CO-N), thio-ester (CO-S) and/or phospho-ester (PO-O) bond. Preferably the ACE inhibitor is of formula **1**



1

wherein

R^1 is H or C_1-C_3 alkyl,

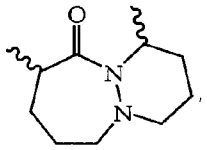
R^2 is C_1-C_3 alkyl optionally substituted with phenyl,

R^3 is C_1-C_5 alkyl optionally substituted with $-NH_2$, or together with R^4 forms an ε-caprolactam derivative optionally containing a sulphur atom and/or a double bond and optionally substituted with -CH=CH-CH=CH- or $-C_4H_3S$,

R^4 is indanyl, or together with R^3 forms an ε-caprolactam derivative as defined above, or together with R^5 forms a pyrrolidine or piperidine derivative optionally containing another nitrogen atom and/or a double bond and optionally substituted with $-SCH_2CH_2S-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2-$, -CH=CH-CH=CH-, $-CH=C(OCH_3)-C(OCH_3)=CH-$, =O or $-CH_3$, and

R^5 is H, or together with R^4 forms a pyrrolidine or piperidine derivative as defined above,

or wherein R^3, R^4 and R^5 together form a bicyclic ring system



The ACE inhibitor may be alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, libenzapril, lisinopril, moexipril, moveltipril, pentopril, perindopril, quinapril, ramipril, rentiapril, spirapril, sosinopril, temocapril, trandolapril or zofenopril, or a pharmaceutically acceptable salt or derivative thereof.

The ACE inhibitor may be alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, fosinopril, imidapril, libenzapril, lisinopril, moexipril, moveltipril, pentopril, perindopril, quinapril, ramipril, rentiapril, spirapril, sosinopril, temocapril, trandolapril or zofenopril, or a pharmaceutically acceptable salt or derivative thereof.

The ACE inhibitor may be benazepril, cilazapril, delapril, fosinopril, imidapril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril or zofenopril, or a pharmaceutically acceptable salt or derivative thereof. The ACE inhibitor may be benazepril, cilazapril, delapril, fosinopril, imidapril, moexipril, perindopril, ramipril, spirapril, trandolapril or zofenopril, or a pharmaceutically acceptable salt or derivative thereof.

Optionally the ACE inhibitor is not enalapril or enalaprilat or a pharmaceutically acceptable salt or derivative thereof. Optionally the ACE inhibitor is not lisinopril or a pharmaceutically acceptable salt or derivative thereof. Optionally the ACE inhibitor is not quinapril or a pharmaceutically acceptable salt or derivative thereof.

Preferably the ACE inhibitor is benazepril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is cilazapril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is delapril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is fosinopril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is imidapril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is moexipril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is quinapril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is ramipril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is spirapril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is trandolapril or a pharmaceutically acceptable salt or derivative thereof. Preferably the ACE inhibitor is zofenopril or a pharmaceutically acceptable salt or derivative thereof. More preferably the ACE inhibitor is perindopril or a pharmaceutically acceptable salt or derivative thereof. Most preferably the ACE inhibitor is perindopril erbumine.

Brief description of the drawings

The present invention will now be described by way of example with reference to the accompanying drawings in which:

Figure 1 schematically depicts the degradation pathways of perindopril erbumine, in particular degradation products B, C, D and F. A list of degradation products and impurities A to I of perindopril erbumine is provided in *European Pharmacopoeia*, 2002, supplement 4.6, pages 4089-4091.

Figure 2 is a graph showing the increase of the diketopiperazine degradation product F on storage of perindopril erbumine with a selection of excipients for 4 weeks at different temperatures and relative humidities.

Detailed description of the invention

It has been found that colloidal silicon dioxide is incompatible with ACE inhibitors, since the presence of colloidal silicon dioxide promotes the degradation of the ACE inhibitors in pharmaceutical compositions.

Colloidal silicon dioxide, also called colloidal anhydrous silica, is sold under trade names such as Aerosil®, Cab-O-Sil®, colloidal silica, fumed silica, fumed silicon dioxide, light anhydrous silicic acid, and silicic anhydride.

Colloidal silicon dioxide is widely used in oral, topical and other pharmaceutical products and is generally regarded as an essentially non-toxic and non-irritant excipient. It is GRAS listed and included in the FDA's Inactive Ingredients Guide.

Without wishing to be bound by theory, it is believed that colloidal silicon dioxide may catalyse the formation of the hydrolytic degradation products and the diketopiperazine degradation products, because colloidal silicon dioxide is acidic, contains water and has a large specific surface area, all of which may promote the hydrolysis of ester, amide, thio-ester and/or phospho-ester bonds required for the formation of the hydrolytic degradation products as well as promote the formation of amide bonds required for the formation of the diketopiperazine degradation products.

Compatibility studies

Compatibility studies were carried out to investigate interactions between ACE inhibitors and commonly used excipients at accelerated storage conditions. Perindopril erbumine of formula **3** was used as exemplary ACE inhibitor.

For the compatibility studies, samples of perindopril erbumine and individual excipients were intimately mixed in equal parts by weight and filled into colourless glass vials, then stoppered with Teflon® plugs and sealed with aluminium seal. The resulting drug/excipient blends were then subjected to the following conditions:

Storage conditions	Storage period
Initial	-
Control: 2-8°C	4 weeks
25°C ± 2°C / 60% ± 5% RH	4 weeks
40°C ± 2°C / 75% ± 5% RH	4 weeks
50°C ± 2°C	4 weeks
60°C ± 2°C	4 weeks

Excipients tested were: Pharmatose DCL 21® which is a lactose; mannitol; Avicel PH 112® which is a microcrystalline cellulose; dibasic calcium phosphate; maize starch; PVP K30® which is a polyvinylpyrrolidone; Aerosil 200® which is colloidal silicon dioxide; talc; Starch 1500® which is a pregelatinised starch; and magnesium stearate.

Initially and after 4 weeks, the drug/excipient blends were checked for their physical appearance and analysed using HPLC.

The physical appearance of the samples of the drug/excipient blends was determined by eye and allocated to one of four categories: no change (NC), very slightly off white (VSOW), slightly off white (SOW), and off white (OW). The physical appearance data obtained are summarised in Table 1.

Blend	Initial	Control: 2-8°C	25°C / 60% RH	40°C / 75% RH	50°C	60°C
Drug = Perindopril erbumine	NC	NC	NC	NC	NC	NC
Drug + Pharmatose DCL 21®	NC	NC	NC	VSOW	SOW	OW
Drug + Mannitol	NC	NC	NC	NC	NC	VSOW
Drug + Avicel PH 112®	NC	NC	NC	NC	VSOW	SOW
Drug + Dibasic calcium phosphate (anhydrous)	NC	NC	NC	NC	VSOW	SOW
Drug + Maize Starch (dried)	NC	NC	NC	NC	VSOW	SOW
Drug + PVP K30®	NC	NC	NC	NC	NC	NC
Drug + Starch 1500®	NC	NC	NC	NC	NC	NC
Drug + Aerosil 200®	NC	NC	NC	NC	NC	NC
Drug + Talc	NC	NC	NC	NC	NC	NC
Drug + Magnesium stearate	NC	NC	NC	NC	NC	NC

Table 1

The HPLC analyses were carried out following the method described in *European Pharmacopoeia* (2002, supplement 4.6, pages 4089-4091) for active pharmaceutical ingredients and related substances. Comparative samples of degradation products B and F, the structure of which is shown in Figure 1, were obtained from the active pharmaceutical ingredient manufacturer and analysed by HPLC using the methodology described in *European Pharmacopoeia* (2002, supplement 4.6, pages 4089-4091). The HPLC data, obtained for impurities B and F and for an impurity of unknown structure with a relative retention time (RRT) of 0.49, are summarised in Table 2 and illustrated in Figure 2.

Blend	Conditions	Assay[a]	Impurity B (%)	Impurity F (%)	Unknown Impurity (%)[b]	Total Impurities (%)
Drug = Perindopril erbumine	Initial		-	0.05	0.04	0.17
	25°C / 60% RH	98.6	-	0.06	0.04	0.17
	40°C / 75% RH	100.3	-	0.12	0.04	0.20
	50°C	100.0	-	0.23	0.05	0.30
	60°C	100.3	-	0.10	0.06	0.40
Drug + Pharmatose DCL 21®	25°C / 60% RH	95.9	-	0.07	0.04	0.18
	40°C / 75% RH	99.1	-	0.16	0.04	0.20
	50°C	100.8	-	0.18	0.04	0.24
	60°C	96.4	-	0.37	0.07	0.40
Drug + Mannitol	25°C / 60% RH	97.3	-	0.05	0.04	0.17
	40°C / 75% RH	93.0	-	0.14	0.04	0.20
	50°C	95.9	-	0.17	0.05	0.25
	60°	94.7	-	0.23	0.07	0.40
Drug + Avicel PH 112®	25°C / 60% RH	96.0	-	0.09	0.03	0.20
	40°C / 75% RH	98.1	-	0.19	0.04	0.25
	50°C	104.1	-	0.27	0.04	0.26
	60°	105.1	-	0.56	0.08	0.70
Drug + Dibasic calcium phosphate (anhydrous)	25°C / 60% RH	106.6	-	0.07	0.04	0.15
	40°C / 75% RH	108.0	-	0.18	0.04	0.20
	50°C	120.9	-	0.19	0.06	0.25
	60°C	118.5	-	0.16	0.09	0.50
Drug + Maize Starch (dried)	25°C / 60% RH	94.7	-	0.07	0.04	0.17
	40°C / 75% RH	97.8	-	0.17	0.04	0.20
	50°C	101.4	-	0.25	0.06	0.25
	60°C	99.6	-	0.42	0.09	0.60
Drug + PVP K30®	25°C / 60% RH	94.7	-	0.07	0.03	0.18
	40°C / 75% RH	99.2	-	0.13	0.03	0.20
	50°C	94.4	-	0.17	0.03	0.25
	60°	90.4	-	0.30	0.05	0.50
Drug + Starch 1500®	25°C / 60% RH	94.8	-	0.06	0.03	0.20
	40°C / 75% RH	97.5	-	0.14	0.04	0.25
	50°C	104.3	-	0.17	0.07	0.30
	60°	93.9	-	0.19	0.04	0.40
Drug + Aerosil 200®	25°C / 60% RH	87.3	-	0.10	0.04	0.30
	40°C / 75% RH	83.9	0.16	0.51	0.16	0.90
	50°C	87.0	0.25	0.86	0.20	1.40
	60°C	77.9	1.33	1.76	0.66	3.50
Drug + Talc	25°C / 60% RH	100.8	-	0.06	-	0.15
	40°C / 75% RH	106.1	-	0.12	-	0.20
	50°C	105.2	-	0.13	0.04	0.25
	60°	101.2	-	0.14	0.08	0.30
Drug + Magnesium stearate	25°C / 60% RH	103.3	-	0.05	0.03	0.15
	40°C / 75% RH	99.0	-	0.05	0.06	0.20
	50°C	100.4	0.03	0.06	0.06	0.25
	60°	107.4	0.14	0.05	0.14	0.40

a – Assay of perindopril against an external standard.
b – Unknown Impurity: Relative Retention Time (RRT) = 0.49.

Table 2

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As can be seen from the results presented in Table 2 and Figure 2, there is a distinct incompatibility between perindopril erbumine and Aerosil 200® (colloidal silicon dioxide) leading to the increased formation of the diketopiperazine impurity F as well as other impurities. The other nine excipients tested, on the other hand, can be seen to be compatible with perindopril erbumine.

Pharmaceutical compositions

In view of the incompatibility between perindopril erbumine and colloidal silicon dioxide, various pharmaceutical formulations were prepared without colloidal silicon dioxide. The compositions of the formulations prepared are shown in Tables 3a and 3b.

The pharmaceutical formulations were prepared by sifting the excipients and the active ingredient, perindopril erbumine. The excipients and the active ingredient were then mixed to obtained the pharmaceutical formulations. Once prepared, the pharmaceutical formulations were compressed into tablets.

Ingredients (mg/tablet)	Example 1	Example 2	Example 3	Example 4	Example 5	Example 6	Example 7
Perindopril erbumine	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Pharmatose DCL 21®	20.0	40.0	60.0	62.5	60.0	57.5	55.0
Avicel PH 112®	60.0	40.0	20.0	20.0	20.0	20.0	20.0
Magnesium stearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Maize starch (dried)	5.0	5.0	5.0	-	-	-	-
Talc	-	-	-	2.5	5.0	7.5	10.0
Total weight	90.0	90.0	90.0	90.0	90.0	90.0	90.0

Table 3a

Ingredients (mg/tablet)	Example 8	Example 9	Example 10	Example 11	Example 12	Example 13	Example 14	Example 15
Perindopril erbumine	4.0	4.0	4.0	4.0	4.0	4.0	4.0	2.0
Pharmatose DCL 21®	62.5	60.0	57.5	55.0	60.5	59.0	58.0	30.0
Avicel PH 112®	17.5	17.5	17.5	17.5	17.5	17.5	17.5	8.75
Magnesium stearate	1.0	1.0	1.0	1.0	0.5	2.0	3.0	0.5
Maize starch (dried)	2.5	5.0	7.5	10.0	5.0	5.0	5.0	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	1.25
Total weight	90.0	90.0	90.0	90.0	90.0	90.0	90.0	45.0

Table 3b

It will be understood that the present invention has been described above by way of example only. The examples are not intended to limit the scope of the invention. Various modifications and embodiments can be made without departing from the scope and spirit of the invention, which is defined by the following claims only.

Claims

1. A stable pharmaceutical composition comprising an ACE inhibitor.

2. A stable pharmaceutical composition of claim 1, further comprising one or more excipients which are compatible with the ACE inhibitor.

3. A stable pharmaceutical composition of claim 2, wherein the excipients are selected from lactose, microcrystalline cellulose, mannitol, dibasic calcium phosphate, maize starch, pregelatinised starch, polyvinylpyrrolidone, talc and magnesium stearate.

4. A stable pharmaceutical composition of any one of the preceding claims, further comprising a glidant which is substantially free of colloidal silicon dioxide.

5. A stable pharmaceutical composition of any one of the preceding claims, wherein the composition is substantially free of colloidal silicon dioxide.

6. A pharmaceutical composition comprising an ACE inhibitor, wherein the composition is substantially free of any acidic excipients having a large specific surface area.

7. A pharmaceutical composition comprising an ACE inhibitor, a diluent, a disintegrant, a glidant and a lubricant, wherein the diluent, disintegrant, glidant and lubricant are compatible with the ACE inhibitor, and wherein the composition is substantially free of colloidal silicon dioxide.

8. A pharmaceutical composition comprising an ACE inhibitor, a diluent, a disintegrant, a glidant and a lubricant, wherein the diluent, disintegrant, glidant and lubricant are compatible with the ACE inhibitor, and wherein the composition is substantially free of any acidic excipients having a large specific surface area.

9. A pharmaceutical composition of claim 7 or 8, wherein the diluent is a cellulose, a carbohydrate, a phosphate or talc.

10. A pharmaceutical composition of any one of claims 7 to 9, wherein the disintegrant is a starch.

11. A pharmaceutical composition of any one of claims 7 to 10, wherein the glidant is a starch or talc.

12. A pharmaceutical composition of any one of claims 7 to 11, wherein the lubricant is an alkali or earth alkaline metal salt of a saturated C_{16-24} carboxylic acid.

13. A pharmaceutical composition of any one of claims 7 to 12, further comprising a binder.

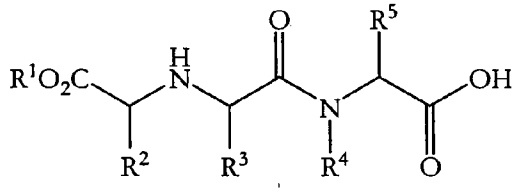
14. A pharmaceutical composition of claim 13, wherein the binder is a starch or polyvinylpyrrolidone.

15. A pharmaceutical composition comprising an ACE inhibitor and four or more excipients selected from lactose, microcrystalline cellulose, mannitol, dibasic calcium phosphate, maize starch, pregelatinised starch, polyvinylpyrrolidone, talc and magnesium stearate, wherein the composition is substantially free of colloidal silicon dioxide.

16. A pharmaceutical composition of claim 15, comprising five, six, seven or more excipients selected from lactose, microcrystalline cellulose, mannitol, dibasic calcium phosphate, maize starch, pregelatinised starch, polyvinylpyrrolidone, talc and magnesium stearate.

17. A pharmaceutical composition of any one of the preceding claims, wherein the ACE inhibitor has an ester (CO-O), amide (CO-N), thio-ester (CO-S) and/or phospho-ester (PO-O) bond.

18. A pharmaceutical composition of any one of the preceding claims, wherein the ACE inhibitor is of formula **1**



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wherein

R^1 is H or C_1-C_3 alkyl,

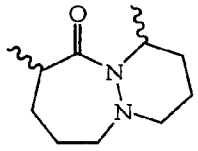
R^2 is C_1-C_3 alkyl optionally substituted with phenyl,

R^3 is C_1-C_5 alkyl optionally substituted with $-NH_2$, or together with R^4 forms an ε-caprolactam derivative optionally containing a sulphur atom and/or a double bond and optionally substituted with -CH=CH-CH=CH- or $-C_4H_3S$,

R^4 is indanyl, or together with R^3 forms an ε-caprolactam derivative as defined above, or together with R^5 forms a pyrrolidine or piperidine derivative optionally containing another nitrogen atom and/or a double bond and optionally substituted with $-SCH_2CH_2S-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2-$, -CH=CH-CH=CH-, $-CH=C(OCH_3)-C(OCH_3)=CH-$, =O or $-CH_3$, and

R^5 is H, or together with R^4 forms a pyrrolidine or piperidine derivative as defined above,

or wherein R^3, R^4 and R^5 together form a bicyclic ring system



19. A pharmaceutical composition of any one of the preceding claims, wherein the ACE inhibitor is alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, imidapril, libenzapril, lisinopril, moexipril, moveltipril, pentopril, perindopril, quinapril, ramipril, rentiapril, spirapril, sosinopril, temocapril, trandolapril or zofenopril, or a pharmaceutically acceptable salt or derivative thereof.

20. A pharmaceutical composition of any one of the preceding claims, wherein the ACE inhibitor is alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, fosinopril, imidapril, libenzapril, lisinopril, moexipril, moveltipril, pentopril, perindopril, quinapril, ramipril, rentiapril, spirapril, sosinopril, temocapril, trandolapril or zofenopril, or a pharmaceutically acceptable salt or derivative thereof.

21. A pharmaceutical composition comprising an ACE inhibitor and three or more excipients selected from lactose, microcrystalline cellulose, mannitol, dibasic calcium phosphate, maize starch, pregelatinised starch, polyvinylpyrrolidone, talc and magnesium stearate, wherein the composition is substantially free of colloidal silicon dioxide, and wherein the ACE inhibitor is alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, fosinopril, imidapril, libenzapril, lisinopril, moexipril, moveltipril, pentopril, perindopril, quinapril, ramipril, rentiapril, spirapril, sosinopril, temocapril, trandolapril or zofenopril, or a pharmaceutically acceptable salt or derivative thereof.

22. A pharmaceutical composition of claim 21, comprising four, five, six, seven or more excipients selected from lactose, microcrystalline cellulose, mannitol, dibasic calcium phosphate, maize starch, pregelatinised starch, polyvinylpyrrolidone, talc and magnesium stearate.

23. A pharmaceutical composition of any one of the preceding claims, wherein the ACE inhibitor is benazepril, cilazapril, delapril, fosinopril, imidapril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril or zofenopril, or a pharmaceutically acceptable salt or derivative thereof.

24. A pharmaceutical composition of any one of the preceding claims, wherein the ACE inhibitor is perindopril or a pharmaceutically acceptable salt or derivative thereof.

25. A pharmaceutical composition of claim 24, wherein the pharmaceutically acceptable salt of perindopril is perindopril erbumine.

26. A pharmaceutical composition of any one of the preceding claims, comprising:

2-8% by weight perindopril erbumine,
20-75% by weight lactose anhydrous,
15-75% by weight microcrystalline cellulose,
0-15% by weight maize starch,
0.5-8% by weight magnesium stearate, and
0-15% by weight talc.

27. A stable pharmaceutical composition comprising perindopril or a pharmaceutically acceptable salt or derivative thereof, and one or more excipients compatible with perindopril or the pharmaceutically acceptable salt or derivative thereof.

28. A pharmaceutical composition comprising perindopril or a pharmaceutically acceptable salt or derivative thereof, and one or more excipients compatible with perindopril or the pharmaceutically acceptable salt or derivative thereof, wherein the composition is substantially free of colloidal silicon dioxide.

29. A pharmaceutical composition comprising perindopril or a pharmaceutically acceptable salt or derivative thereof, and one or more excipients compatible with perindopril or the pharmaceutically acceptable salt or derivative thereof, wherein the composition is substantially free of any acidic excipients having a large specific surface area.

30. A pharmaceutical composition of any one of claims 27 to 29, wherein the pharmaceutically acceptable salt of perindopril is perindopril erbumine.

31. A pharmaceutical composition of any one of claims 27 to 30, comprising two, three, four, five, six or more different excipients compatible with perindopril or the pharmaceutically acceptable salt or derivative thereof.

32. A pharmaceutical composition of any one of claims 27 to 31, wherein the excipient or excipients are selected from lactose, microcrystalline cellulose, mannitol, dibasic calcium phosphate, maize starch, pregelatinised starch, polyvinylpyrrolidone, talc and magnesium stearate.

33. A stable pharmaceutical composition comprising ramipril or a pharmaceutically acceptable salt or derivative thereof, and one or more excipients compatible with ramipril or the pharmaceutically acceptable salt or derivative thereof.

34. A pharmaceutical composition comprising ramipril or a pharmaceutically acceptable salt or derivative thereof, and one or more excipients compatible with ramipril or the pharmaceutically acceptable salt or derivative thereof, wherein the composition is substantially free of colloidal silicon dioxide.

35. A pharmaceutical composition comprising ramipril or a pharmaceutically acceptable salt or derivative thereof, and one or more excipients compatible with ramipril or the pharmaceutically acceptable salt or derivative thereof, wherein the composition is substantially free of any acidic excipients having a large specific surface area.

36. A pharmaceutical composition of any one of claims 33 to 35, comprising ramipril.

37. A pharmaceutical composition of any one of claims 33 to 35, comprising two, three, four, five, six or more different excipients compatible with ramipril or the pharmaceutically acceptable salt or derivative thereof.

38. A pharmaceutical composition of any one of claims 33 to 37, wherein the excipient or excipients are selected from lactose, microcrystalline cellulose, mannitol, dibasic calcium phosphate, maize starch, pregelatinised starch, polyvinylpyrrolidone, talc, magnesium stearate, glycerol dibehenate, sodium starch glycolate and sodium stearyl fumarate.

39. A pharmaceutical composition of any one of claims 33 to 38, comprising glycerol dibehenate.

40. A pharmaceutical composition of any one of the preceding claims, further comprising a β-blocker, a diuretic, a calcium-channel blocker, a vasodilator anti-hypertensive drug, or an angiotensin II receptor antagonist.

41. A pharmaceutical composition of any one of the preceding claims, wherein the composition is suitable for oral, parental, transdermal, airway, rectal, vaginal or topical administration.

42. A pharmaceutical composition of claim 41, wherein the composition is suitable for oral administration.

43. A pharmaceutical composition of claim 42, wherein the composition is provided in the form of a tablet, capsule, caplet, troche, lozenge, powder or granules.

44. A pharmaceutical composition of claim 42 or 43, wherein the composition is in unit dosage form comprising 2-20mg of the ACE inhibitor.

45. A pharmaceutical composition substantially as hereinbefore described with reference to the description.

46. A pharmaceutical composition of any one of the preceding claims, for use as a medicament.

47. A pharmaceutical composition of claim 46 for use as a medicament for the treatment or prevention of a cardiovascular disorder, hypertension, coronary heart disease or a cerebrovascular disease.

48. A method of treating or preventing a cardiovascular disorder, hypertension, coronary heart disease or a cerebrovascular disease, comprising administering an effective amount of a pharmaceutical composition of any one of claims 1 to 47 to a patient in need thereof.

49. Use of a pharmaceutical composition of any one of claims 1 to 47 in the manufacture of a medicament for the treatment or prevention of a cardiovascular disorder, hypertension, coronary heart disease or a cerebrovascular disease.

50. A method of preparing a pharmaceutical composition of any one of claims 1 to 47, comprising the step of blending the ACE inhibitor with the excipients.

51. A method of claim 50, wherein the pharmaceutical composition is prepared in batches of 5-150kg.

52. A method of providing a stable pharmaceutical composition comprising an ACE inhibitor, the method comprising providing the composition substantially free of colloidal silicon dioxide.

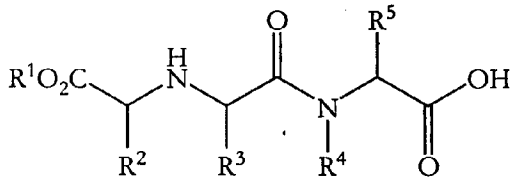
53. Use of a substantial absence of colloidal silicon dioxide to provide a stable pharmaceutical composition comprising an ACE inhibitor.

54. Use of one or more excipients to provide a stable pharmaceutical composition comprising an ACE inhibitor, wherein the composition is substantially free of colloidal silicon dioxide.

55. A method of claim 52 or a use of claim 53 or 54, wherein the pharmaceutical composition is stabilized to minimize the degradation of the ACE inhibitor.

56. A method or use of any one of claims 52 to 55, wherein the ACE inhibitor has an ester (CO-O), amide (CO-N), thio-ester (CO-S) and/or phospho-ester (PO-O) bond.

57. A method or use of any one of claims 52 to 56, wherein the ACE inhibitor is of formula **1**



1

wherein

R^1 is H or C_1-C_3 alkyl,

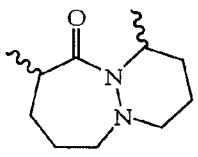
R^2 is C_1-C_3 alkyl optionally substituted with phenyl,

R^3 is C_1-C_5 alkyl optionally substituted with $-NH_2$, or together with R^4 forms an ε-caprolactam derivative optionally containing a sulphur atom and/or a double bond and optionally substituted with -CH=CH-CH=CH- or $-C_4H_3S$,

R^4 is indanyl, or together with R^3 forms an ε-caprolactam derivative as defined above, or together with R^5 forms a pyrrolidine or piperidine derivative optionally containing another nitrogen atom and/or a double bond and optionally substituted with $-SCH_2CH_2S-$, $-CH_2CH_2CH_2CH_2-$, $-CH_2CH_2CH_2-$, -CH=CH-CH=CH-, $-CH=C(OCH_3)-C(OCH_3)=CH-$, =O or $-CH_3$, and

R^5 is H, or together with R^4 forms a pyrrolidine or piperidine derivative as defined above,

or wherein R^3, R^4 and R^5 together form a bicyclic ring system



58. A method or use of any one of claims 52 to 57, wherein the ACE inhibitor is alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, enalapril, enalaprilat,

fosinopril, imidapril, libenzapril, lisinopril, moexipril, moveltipril, pentopril, perindopril, quinapril, ramipril, rentiapril, spirapril, sosinopril, temocapril, trandolapril or zofenopril, or a pharmaceutically acceptable salt or derivative thereof.

59. A method or use of any one of claims 52 to 58, wherein the ACE inhibitor is alacepril, benazepril, captopril, ceronapril, cilazapril, delapril, fosinopril, imidapril, libenzapril, lisinopril, moexipril, moveltipril, pentopril, perindopril, quinapril, ramipril, rentiapril, spirapril, sosinopril, temocapril, trandolapril or zofenopril, or a pharmaceutically acceptable salt or derivative thereof.

60. A method or use of any one of claims 52 to 59, wherein the ACE inhibitor is benazepril, cilazapril, delapril, fosinopril, imidapril, moexipril, perindopril, quinapril, ramipril, spirapril, trandolapril or zofenopril, or a pharmaceutically acceptable salt or derivative thereof.

61. A method or use of any one of claims 52 to 60, wherein the ACE inhibitor is perindopril or a pharmaceutically acceptable salt or derivative thereof.

62. A method or use of claim 61, wherein the pharmaceutically acceptable salt of perindopril is perindopril erbumine.

Application No: GB0329232.3 **Examiner:** Mr Stephen Quick

Claims searched: 1-62 **Date of search:** 23 March 2004

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular reference
X	1-8, 27-29, 33-35, 45, 46, 49, 50 & 52-54 at least	US 5151433 A (HOECHST), see especially tables 1-3, examples 4-8, 11 & 12, column 1 lines 1-43 and column 4 line 48ff
X	1-3, 5, 6, 33-35, 45, 46, 49, 50 & 52-54 at least	WO 2002/011709 A2 (HEXAL), see especially examples 1-10 and page 1 line 2
X	1-8, 15, 21, 27-29, 33-35, 45, 46, 49, 50 & 52-54 at least	WO 2003/075842 A2 (TEVA PHARMACEUTICALS), see especially examples 1-4, page 1 lines 16-28 and page 6 lines 3-9 & 24-27
X	1-8, 21, 45, 46, 49, 50 & 52-54 at least	US 5006344 A (E R SQUIBB & SONS), see especially examples 1-15 and column 1 lines 14-19
X	1-6, 45, 46, 49, 50 & 52-54 at least	US 5562921 A (B C SHERMAN), see especially column 4 examples #2-#6 (allowing for obvious tabulation error) and column 1 lines 8-10; acknowledged in this application
X	1, 2, 5, 6, 45, 46, 49, 50 &	US 5433951 A (BRISTOL-MYERS SQUIBB), see especially column 6 examples 1-10 (particularly table I and column 3 line 63ff) and column 1 lines 12-17

	52-54 at least	
X	5 at least	EP 0264887 A1 (WARNER-LAMBERT), see especially the example
X	5 at least	WO 03/059330 A1 (RANBAXY LABORATORIES), see especially tables I-V
X	5 at least	WO 03/028707 A1 (B C SHERMAN), see especially examples 1-4

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^{W} :

Worldwide search of patent documents classified in the following areas of the IPC^{07}

A61K

The following online and other databases have been used in the preparation of this search report

EPODOC, JAPIO, WPI